REMARKS/ARGUMENTS

Reexamination and reconsideration of this Application, withdrawal of the rejections, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the above claim amendments and remarks that follow.

Claims 1-25 and 38-40 have been canceled without prejudice as being directed to non-elected subject matter. Claims 26 and 34-37 have been amended to recite that the crystallized dextran microparticles are porous and have a porosity of at least 10% by volume. Support for this amendment can be found at page 5 of the specification. Claim 26 has further been amended to remove reference to dosing. Claim 27 has been amended to remove language relating to microparticle size and the physical relation of the insulin to the microparticles. Said language has been re-introduced as new claims 41 and 42. New claims 41-45 have been added, and Applicants submit no new matter has been introduced by said new claims. Claims 26-37 and 41-45 are pending.

Claims 26-27, 29-32, and 36-37 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 4,713,249 to Schröder in view of U.S. Patent No. 4,963,526 to Ecanow. Applicants respectfully traverse this rejection.

Independent claim 26 recites a pharmaceutical composition comprising porous crystallized dextran microparticles having a porosity of at least 10% by volume and a therapeutically effective amount of insulin. Applicants respectfully submit that neither Schröder nor Ecanow, alone or in combination, disclose or suggest such a composition.

Schröder is solely directed to enclosing (*i.e.*, encapsulating) biologically active substances. In describing the prior art, Schröder discloses that polymers useful for delivering biologically active substances "should be able to enclose and release substances of different molecular weights" (column 2, lines 18-19). At column 3 (lines 59-61), Schröder discloses that its invention "describes how one prepares crystallised carbohydrate spheres with enclosed biologically active substances".

In light of the above, it is clear that Schröder is directed to the formation of carbohydrate capsules encapsulating an active substance. This in no way discloses or suggests the composition of claim 26 comprising porous crystallized dextran microparticles having a porosity of at least 10% by volume and a therapeutically effective amount of insulin. Clearly, Schröder

does not expressly disclose porous dextran microparticles having a porosity of at least 10% by volume. Moreover, nothing in Schröder can be pointed to as suggesting that providing porous dextran microparticles having the defined porosity would be useful.

The carbohydrate spheres of Schröder enclosing an active substance are prepared according to a specific emulsification process and are designed to contain the active substance until the spheres are degraded. Thus, in a degrading environment, the spheres would degrade releasing all of the active agent contained therein.

At column 3 (line 59) through column 4 (line 37), Schröder describes how the encapsulated active substance is prepared. The carbohydrate is dissolved in a solvent having a specific dielectric constant, and the biologically active substance is added. The mixture is then emulsified in an emulsion system comprising the solution and an emulsion medium consisting of a liquid that is immiscible with the solution and which contributes to the formation of droplets of the carbohydrate solution in the emulsion medium. The emulsified droplets are then transferred to a liquid capable of crystallizing the droplets out of solution to form carbohydrate spheres with the biologically active substance enclosed therein (column 4, lines 28-33). This detailed process is necessary according to Schröder to prepare the spheres enclosing the active substance so that the active substance can be released by degradation of the spheres. Such process of preparing capsules enclosing an active substance and the method of action of the capsules in no way teaches or suggests the present invention.

At page 5 of the present specification, the dextran microparticles are disclosed as having a porosity of at least 10% by volume. Thus, the structure comprises microporous microparticles with areas of macroporosity located between the particles. At page 19, the specification goes on to point out that the insulin can be located in micropores in the microparticles and/or in macropores between the microparticles. At page 20, the specification further points out that the microparticles are crystallized prior to being combined with the insulin such that the insulin can be located in contact with a surface of the microparticles and/or in pores of the microparticles. At page 26, the present specification points out that the microparticles have sufficient porosity to contain the therapeutic agent within the pores and provide a timed release of the therapeutic agent from the pores.

Accordingly, Applicants submit that just as Schröder fails to expressly disclose porous dextran microparticles having a porosity of at least 10% by volume, Schröder also fails to teach or suggest such microparticles because the method of forming the carbohydrate encapsulated active in Schröder, and the method of action thereof, fails to disclose or suggest the presently claimed composition. In other words, one of skill in the art viewing Schröder would find no motivation to prepare a combination of porous crystallized dextran microspheres having a porosity of at least 10% by volume and insulin because the porosity of the carbohydrate spheres in Schröder is not disclosed as being relevant to the method of preparation or the mode of action thereof. The key component of Schröder is being able to emulsify the carbohydrate and active agent to form droplets encapsulating the active agent so it can be released by degradation of the carbohydrate sphere. This in no way teaches that porosity is relevant.

More particularly, Schröder in no way teaches that by providing its carbohydrate spheres with a defined porosity is useful for causing timed release of an active agent because the active agent of Schröder is completely encapsulated by the carbohydrate sphere. As pointed out above, the carbohydrate spheres of Schröder degrade to release the active agent and do not provide the timed release provided according to the present invention. The Examiner has pointed to no specific teaching or disclosure in Schröder that would motivate a skilled artisan to make porous crystallized dextran microparticles having a porosity of at least 10% by volume. This is a distinct physical characteristic of the dextran microparticles, and the microparticles must be specifically prepared to have such a porosity. Schröder provides no teaching that such porosity would be useful, and a skilled person simply would not arrive at the presently claimed invention absent the benefit of the present disclosure. Schröder simply does not pave the way to the present invention.

Accordingly, Applicants submit there is no teaching or suggestion in Schröder that would lead the skilled artisan to the composition of claim 26. Applicants further submit this is also the case with the compositions of claims 36 and 37, which also recite porous crystallized dextran microparticles having a porosity of at least 10% by volume.

Applicants further submit that the combination of Ecanow fails to remedy the shortcomings of Schröder. Ecanow is directed to a two phase coacervate system wherein a relatively non-polar coacervate phase is in equilibrium with a relatively polar liquid aqueous

phase. Ecanow nowhere disclose forming crystallized dextran microparticles. Further, Ecanow certainly does not disclose or suggest that crystallized dextran microparticles having a porosity of at least 10% by volume would be useful in preparing a pharmaceutical composition. Accordingly, Applicants respectfully submit that Schröder and Ecanow, alone or in combination, fail to disclose or suggest the compositions of the presently rejected claims, and Applicants respectfully request reconsideration and withdrawal of the present rejection.

Applicants also respectfully point out that Schröder and Ecanow, alone or in combination, fail to disclose or suggest the compositions of new claims 41-45. Claims 43 and 44 specifically recite compositions of crystallized dextran microparticles and insulin wherein the insulin is not encapsulated by the microparticles. As pointed out above, Schröder only discloses or suggests encapsulation, and Ecanow is only directed to coacervate systems. Claim 45 specifically recites a composition comprising porous crystallized dextran microparticles having a porosity of at least 10% by volume and a therapeutically effective amount of insulin, wherein the insulin is not encapsulated by said microparticles, and wherein the insulin is located in contact with a surface of the porous crystallized dextran microparticles or in pores of the microparticles. Neither Schröder nor Ecanow disclose or suggest such a composition. Accordingly, Applicants respectfully submit claims 41-45 are both novel and non-obvious over Schröder and Ecanow.

Claims 28 and 33-35 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Schröder and Ecanow in view of Moriyama *et al.* (*Journal of Controlled Release* (1996) 42:237-248). Applicants respectfully traverse this rejection.

The rejected claims either recite or depend upon claims that recite compositions comprising porous crystallized dextran microparticles having a porosity of at least 10% by volume and insulin. As pointed out above, neither Schröder nor Ecanow, alone or in combination, disclose or suggest compositions comprising such porous dextran microparticles. Applicants further submit that Moriyama *et al.* fail to remedy this shortcoming. Moriyama *et al.* disclose hydrogels formed of methacrylic dextran (MA-dextran) and PEG. As disclosed at page 239, Moriyama *et al.* disclose that MA-dextran and PEG are solubilized, insulin is added to the solution, and the final mixture is crosslinked to form a gel. Moriyama *et al.* nowhere disclose or suggest that dextran can be formed into porous crystallized microparticles having a defined porosity, and a skilled artisan with the benefit of Moriyama *et al.* would have no motivation to

modify Schröder and/or Ecanow to make porous crystallized dextran microparticles having a porosity of at least 10% by volume. Accordingly, Applicants respectfully submit the rejected claims are not obvious over the cited combination of references, and Applicants respectfully request reconsideration and withdrawal of the rejection.

Applicant respectfully submits that all claims, as now submitted, are in condition for immediate allowance. Accordingly, a Notice of Allowance is respectfully requested in due course. If any minor formalities need to be addressed, the Examiner is directed to contact the undersigned attorney by telephone to facilitate prosecution of this case.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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